Table 1

(@270 days)	SES (N=533)	Control (N=525)	P-value
Death	0.9%	0.6%	ns
MI (all)	2.8%	3.2%	ns
Stent thrombosis (all)	0.4%	0.8%	ns
TLR	4.1%	16.6%	<0.001
TVR (non-TL)	3.2%	4.8%	ns
MACE	7.1%	18.9%	<0.001
TVF	8.6%	21.0%	<0.001

TLR = target lesion revascularization, TVR = target vessel revascularization, MACE = major adverse cardiac events, TVF = target vessel failure

10:00 a.m.

805-4 **Late Incomplete Stent Apposition Following Sirolimus-Eluting Stent: Serial Quantitative Intravascular Ultrasound Analysis From the SIRIUS Trial**

Junya Ako, Yoshihiro Morino, Yasuhiro Honda, Shinjo Sonoda, Mitsuyasu Terashima, Ali Hassan, Martin B. Leon, Jeffrey W. Moses, Steve Osterle, Charles L. Brown, Donald S. Baim, Paul G. Yock, Peter J. Fitzgerald, the SIRIUS Investigators, Stanford University, Stanford, CA, Lenox Hill Hospital, New York, NY

Background: Stent incomplete apposition (IA) at follow-up is reported in drug-eluting stents. The aim of this study was to clarify the morphometric IVUS characteristics of late IA as compared with persistent IA following sirolimus-eluting stents (SES) vs bare metal stents (BMS).
Methods: IVUS data were obtained from SIRIUS, a prospective, randomized, multicenter trial. IA was defined as >1 struts separated from vessel wall with evidence of blood speckle behind the struts. The maximal stent/lumen gap, maximal axial length, and arc degrees of incompletely apposed struts were quantified. IA index was defined as total lumen area divided by lumen area within the stent. Persistent IA was considered present when IA was observed at both baseline and 8-month follow-up. Late IA was defined as new IA detected only at follow-up.
Results: Of 130 serial cases, there were 19 follow-up IA segments in 17 patients (BMS 6, SES 11) available for quantitative analysis. While persistent IA was observed in both groups (BMS 6, SES 4), late IA was seen only in SES. ΔVessel area was significantly larger in late IA than persistent IA ($p<0.05$), and 3 late IAs showed pathologic positive remodeling (>20% increase in vessel area compared to baseline). All persistent IAs were located at stent edges, whereas 77% of late IAs occurred at single or multiple mid-stent segments ($p<0.05$).
Conclusions: The characteristic morphometric findings of late IA following SES may suggest different vessel wall biology of this phenomenon compared to persistent IA.

	persistent IA BMS (n=6)	persistent IA SES (n=4)	late IA SES (n=9)
Gap, mm^2	0.36±0.17	0.40±0.12	0.69±0.33
Arc, °	107±22.5	97±14.0	145±53.1
Length, mm	1.9±0.65	2.8±1.7	4.2±3.4
Follow-up lumen area, mm^2	8.3±2.5	9.8±1.4	11.0±2.8
Follow-up vessel area, mm^2	19.0±7.3	17.0±2.5	18.9±3.6
Δvessel area, mm^2	-0.007±0.61	0.34±0.88	2.6±1.0
IA index	1.1±0.07	1.1±0.02	1.3±0.36

10:15 a.m.

805-5 **Do Overlapping Multiple Sirolimus-Eluting Stents Impact Angiographic and Clinical Outcomes? Insights From the SIRIUS Trial**

Giora Weisz, Jeffrey W. Moses, Jeffrey J. Popma, Greg Mishkel, Robert L. Wilensky, Barry Cohen, Hooman Madyoon, David Roberts, Martin B. Leon, Lenox Hill Hospital Heart and Vascular Institute of New York and Cardiovascular Research Foundation, New York, NY

Background: Although previous clinical studies have demonstrated a dramatic reduction in subsequent restenosis (Res) after sirolimus-eluting stent (SES) implantation, little is known about the impact of overlapping multiple stents on angiographic and clinical outcomes. **Methods**: In the randomized, double-blind SIRIUS trial, in longer lesions or to treat edge dissections, multiple overlapping stents were implanted in 33% of the SES pts (n=176) and in 32% of the control bare stent (CS) pts (n=168). Clinical and angiographic findings, including the contribution of the overlap region to Res, were assessed. **Results:** Overlap SES and CS pts had similar reference vessel diameter (2.77 vs 2.80 mm), lesion length (18.2 vs 18.1 mm), pre-treatment minimal luminal diameter (0.93 vs 0.94 mm), stent length (28.3 vs 27.8 mm), and stent overlap-segment length (4.6 vs 4.1 mm). There were no differences in safety outcomes including in-hospital MACE (4.5% vs 4.2%), subacute stent thrombosis (1 pt in each group, 0.6%), late stent thrombosis (none), and aneurysms (none). Angiographic and clinical efficacy were significantly better ($p<0.001$) in the SES vs. CS pts: in-lesion late loss (0.20 vs 0.93 mm), in-lesion binary restenosis (8.8% vs 42.7%), target lesion revascularization (4.7% vs 8.3%), and MACE (8.6% vs 23.1%). Eight pts in the overlap SES group had Res within the stent margins; one case was subacute stent thrombosis, one case was focal and not at the overlap region, one had diffuse Res (3 undersized stents after severe dissection), and the five remaining cases had focal Res within the overlap region. **Conclusions**: Overlapping SES vs. CS in the SIRIUS trial was associated with (1) infrequent adverse clinical outcomes (death, MI, stent thrombosis, or aneurysms), (2) maintained striking improvement for SES in all efficacy measures, and (3) the site of SES Res was usually within the stent at the overlap region. Factors such as vessel tortuosity, local flow disturbances, drug dosing effects or stent-edge incomplete apposition may contribute to this apparent increased overlap zone Res, which may be partially resolved with the use of longer single SES and IVUS guidance.

ORAL CONTRIBUTIONS

808 Restenosis: Basic Mechanisms

Monday, March 31, 2003, 9:15 a.m.-10:30 a.m.
McCormick Place, Room S403

9:15 a.m.

808-1 **Mobilized Bone Marrow Stem Cells Accelerate Reendothelialization, Reduce Vascular Inflammation, and Prevent Restenosis After Intravascular Radiation**

Hyun-Jai Cho, Hyo-Soo Kim, Dae-Hee Kim, Seil Oh, In-Ho Chae, Byung-Hee Oh, Myoung-Mook Lee, Young-Bae Park, Yun-Shik Choi, Seoul National University College of Medicine, Seoul, South Korea, Clinical Research Institute, Seoul National University Hospital, Seoul, South Korea

Background: Stem cell therapy may provide new possibilities for the treatment of vascular disorders. We investigated a role of mobilized stem cell in the healing process after intravascular radiation, the condition of few replicating endothelial cells in adjacent area. **Methods:** 1% cholesterol diet fed male New Zealand White rabbits with injured iliac artery were divided into two groups. The GM-CSF group (n=15) received rhGM-CSF (60μg/day) daily for 1 week, beginning 7 day before injury. Control group (n=18) received human albumin. One iliac artery was subjected to intravascular radiation via ^{188}Re-balloon and the contralateral iliac artery to balloon angioplasty control. Morphometry and immunohistochemistry were done. Peripheral blood mononuclear cells (MNCs) were isolated from blood just before vessel harvest, analyzed FACS and cultured for 4 weeks. **Results:** In control group, intravascular radiation therapy reduced neointimal hyperplasia (0.09±0.03 vs 0.26±0.11 mm^2, $P<0.01$) but delayed reendothalialization and promoted inflammatory cell infiltration. After GM-CSF pretreatment, reendothelialization index (defined as CD31 stained endoluminal perimeter) recovered to 81±13 % (n=7), whereas 30±11 % in the control radiation group (n=9) ($P<0.01$) and RAM11-positive cell (macrophage) infiltration reduced in media at 14 days. (12±7 vs 29±10 %, $P<0.01$) Also, additional significant reduction in neointimal thickening was observed. (0.04±0.01 vs 0.09±0.03 mm^2, $P<0.01$) FACS analysis showed that 24% of MNCs were positive for CD31 and 13% positive for CD34 in the GM-CSF group but all negative in the control group. Cultured cells were assayed with costaining with DiI/acLDL and FITC-conjugated BS Lectin as endothelial progenitor cells, also double positive stained cell count was significant higher in GM-CSF group. (33±15 vs 6±4 /mm^2, 2 weeks; 446±101 vs 58±29 / mm^2, 4 weeks after culture, $P<0.01$) **Conclusions:** GM-CSF pretreatment mobilizes stem cells, accelerates reendothelialization and reduces inflammatory cells infiltration after intravascular radiation therapy, which suggests that stem cell therapy is a promising strategy for enhancing vascular healing process after angioplasty.

9:30 a.m.

808-2 **Activation of Peroxisome Proliferator-Activated Receptor and Gamma Inhibits Neointimal Formation in a Diabetic Rat Carotid Artery Injury Model**

Kai Wang Liming Fan, Zhongmin Zhou, Farhad Forudi, Xiaorong Zhou, A. Michael Lincoff, Eric J. Topol, Marc S. Penn, The Cleveland Clinic Foundation, Cleveland, OH

Background: Peroxisome Proliferator-Activated Receptor γ (PPARγ) is member of the nuclear receptor superfamily of ligand-dependent transcription factors. Thiazolidinediones, which are anti-diabetic agents and high-affinity ligands for PPARγ, have been shown to inhibit the growth of vascular smooth muscle cells. In this study, the role of PPARγ on neointimal formation was studied in a diabetic rat carotid artery injury model. **Methods and Results:** Balloon injury of carotid artery was performed in the Zucker fat rats (diabetic) and lean rats (non-diabetic) using the standard method. In treatment groups, rosiglitazone (20mg/kg/day), PPARγ agonist, was given orally 1 week before injury through the 21 days follow-up. The animals were sacrificed after 21 days, and morphometric analysis was performed. Lipids and glucose assay was performed at baseline and 21 days. Neointimal formation was significantly decreased by the administration of rosiglitazone, but only in the diabetic rat cohort (Table). There was no difference of lipids and glucose levels between baseline and 21 days in the diabetic rats. **Conclusion:** The activation of PPARγ inhibits neointimal hyperplasia in a diabetic rat carotid artery injury

model, highlighting this receptor's potential role in the prevention of restenosis in the diabetic patients..

Table. Morphometric Data

	Zucker fat rats		Zucker lean rats	
	Placebo (n=12)	Treatment (n=8)	Placebo (n=10)	Treatment (n=7)
Luminal area (mm^2)	0.15±0.05	0.22±0.06*	0.21±0.04	0.23±0.04
Neointimal Area (IA, mm^2)	0.21±0.05	0.15±0.05*	0.14±0.06	0.12±0.03
Medial Area (MA, mm^2)	0.10±0.01	0.10±0.01	0.11±0.03	0.10±0.01
External Elastic Lamina (mm^2)	0.45±0.05	0.47±0.05	0.46±0.05	0.44±0.04
IA/MA	2.10±0.47	1.43±0.47*	1.21±0.41	1.21±0.30

* P< 0.05 when compared with placebo.

9:45 a.m.

808-3 **Vascular Injury Induces Expression of Periostin: A Novel Vascular Extracellular Matrix Protein via the PI3-Kinase-MAP Kinase Pathway**

Guohong Li, David Wang, Yiu-Fai Chen, Suzanne Oparil, University of Alabama at Birmingham, Birmingham, AL

Periostin (PN, also known as osteoblast-specific factor-2, OSF2), is a novel cell adhesion protein secreted by osteoblasts and osteoblast-like cell lines that has been described in the embryonic heart but not in adult cardiovascular tissues. Based on previous findings from our laboratory and others that extracellular matrix (ECM) proteins such as osteopontin (OPN) play an important role in vascular remodeling following endoluminal injury, we tested the hypotheses that PN is expressed in arteries in the setting of acute vascular injury and explored the signaling mechanisms involved using rat aortic smooth muscle cells (RASMCs) in vitro. Sprague Dawley rats (male, 10-wk old) were subjected to balloon injury of the right carotid artery and sacrificed at 3 days (n=7) and 7 days (n=6) post injury. Uninjured right carotid arteries from sham-operated rats were used as controls (n = 6). PN and OPN mRNA expression was analyzed by Northern blot. PN and OPN mRNA were undetectable in uninjured control vessels but increased post injury, with a peak at 3 days. PN mRNA expression in cultured RASMCs was robustly stimulated by growth factors (10 ng/ml of FGF-1, PDGF-BB) and angiotensin II (100 nM), (2.5-, 2-, and 3.2- fold increases), respectively. This stimulatory effect was completely inhibited by pretreatment with either the PI3 kinase inhibitor (LY294002, 10 uM) or the MAP kinase inhibitor (U0126, 5 uM). In contrast, OPN mRNA expression was not affected by LY294002 and only partially (50%) inhibited by U0126. This study provides a first demonstration that vascular injury induces PN expression, likely via the PI3-kinase- MAP kinase pathway, suggesting a contribution of this novel ECM protein to neointima formation following vascular injury.

10:00 a.m.

808-4 **Systemic Markers of Inflammation Do Not Predict Coronary In-Stent Restenosis in Stable Angina Patients Treated With HMG CoA Reductase Inhibitors**

Abuzeid Gomma, Gideon Hirschfield, June Gallimore, Gordon Lowe, Mark Pepys, Kim Fox, National Heart and Lung Institute and Royal Brompton Hospital, London, United Kingdom, Royal Free and University College Medical School, London, United Kingdom

Introduction: C-reactive protein (CRP), serum amyloid A protein (SAA), and interleukin-6 (IL-6), can predict coronary restenosis following angioplasty and stent deployment. In view of the anti-inflammatory activity of HMG CoA reductase inhibitors (statins), we reviewed this association in statin treated stable angina patients, undergoing angioplasty and stenting. **Methods:** We investigated this association in 182 stable angina patients, in whom 152 underwent elective coronary artery stenting and a further 30, diagnostic angiography alone. Of the patients as a whole, 80% were receiving HMG CoA reductase inhibitors. At 6 months 133 stented patients were restudied and the target lesions quantified. Baseline and serial CRP, SAA and IL-6 values were measured by high sensitivity immunoassays; values are reported as medians. **Results:** The binary restenosis rate at follow-up was 33.8%. There were no significant differences in values of CRP, SAA or IL-6 between patients with or without in-stent restenosis. Patients with pre-procedural values of CRP, SAA or IL-6 greater than the median, continued to have elevated values at follow up.Pre-procedural values of CRP and SAA did not differ between patients undergoing angiography alone or angioplasty plus stenting (CRP: 3.7mg/l vs 3mg/l; SAA: 4.1mg/l vs 3.5mg/l), despite a small difference in values of IL-6 (1.92pg/ml vs 2.78pg/ml, P=0.02). Pre-procedural values of CRP, but not SAA or IL-6, correlated positively with BMI (P=0.01). Higher values of CRP (5.95 mg/l vs 2.95mg/l, P=0.09) and SAA (4.9mg/l vs 3mg/l, P=0.026) were seen in women, while smokers or ex-smokers had elevated values of CRP (3.85mg/l vs 2.15mg/l, P<0.001). **Conclusion:** Pre- or peri-procedural values of CRP, SAA or IL-6, are not associated with coronary in-stent restenosis in stable angina patients in contrast to previous report in patients predominantly with unstable angina. In addition to differences in pathobiology between stable and unstable coronary syndromes, the widespread use of statins with anti-inflammatory activity, reflected by suppression of CRP production, may mask the association.

10:15 a.m.

808-5 **Obligate Role of Macrophage Colony-Stimulating Factor for the Development of Neointimal Thickening Following Arterial Injury**

Tripathi B. Rajavashisth, Ming Liu, Hiroyuki Tanaka, Jagannath Tripathi, Pinky Tripathi, Arthur Loussararian, Peter Libby, Hiroyasu Uzui, Aatish Kumar, Terence M. Doherty, Bojan Cercek, Sanjay Kaul, Prediman K. Shah, Cedars-Sinai Medical Center, Los Angeles, CA, Brigham & Women's Hospital and Harvard Medical School, Boston, MA

Although evidence suggests that macrophage-colony stimulating factor (M-CSF) participates critically in atherosclerosis, little is known about the role of M-CSF in the development of neointimal hyperplasia following mechanical vascular injury. We examined the expression of M-CSF and its receptor, *c-fms*, in rodent and rabbit models of arterial injury. Injured rat carotid arteries expressed 3- to 10-fold higher levels of M-CSF and *c-fms* mRNA within 24 hours following balloon injury as compared to uninjured arteries. The levels of mRNA paralleled the expression of immunoreactive M-CSF and *c-fms* protein. In the rabbit, M-CSF protein expression was greatest in neointimal smooth muscle cells (SMCs) post injury, with some expression also observed in medial SMCs. M-CSF-positive neointimal and medial SMCs exhibited markers of proliferation. At 30 days post injury, neointimal SMCs in the adjacent healed area near the border between injured and uninjured zone lost both proliferative activity and overexpression of M-CSF. The presence of induced M-CSF and *c-fms* expression correlated with the initiation of SMCs proliferation. We, therefore, investigated *in vitro* the effect of exogenous M-CSF on the proliferation of cultured human aortic SMCs (HASMCs). Recombinant human M-CSF stimulated an increase in the incorporation of [^{3}H] thymidine in HASMCs in a concentration-dependent manner, and this effect was inhibited by a rat monoclonal antibody specific to the cell surface epitope of human *c-fms*. The presence of *c-fms* transcript and protein in HASMCs was demonstrated by Northern and Western blot analysis, respectively. To test further the role of M-CSF in vivo, we induced arterial injury by placing a periadventitial cuff around the carotid arteries in compound mutant mice lacking apolipoprotein (apo) E and M-CSF. Homozygous loss of M-CSF (the *op* mutation) abolished the neointimal hyperplastic response to arterial injury in apo E knockout mice. Local delivery of M-CSF to the injured artery restored neointimal proliferation. Taken together, our experimental studies suggest a critical role for M-CSF signaling through *c-fms* for neointimal thickening in response to arterial injury.

ORAL CONTRIBUTIONS

813 Predictors of Restenosis After Stent Placement

Monday, March 31, 2003, 11:00 a.m.-12:15 p.m.
McCormick Place, Room S401

11:00 a.m.

813-1 **Elevated Baseline C-Reactive Protein is Associated With Increased Risk of Death and Myocardial Infarction at One Year Following Percutaneous Coronary Intervention**

Joel P. Reginelli, David S. Lee, Derek P. Chew, Ivan P. Casserly, Kent Dauterman, Kent W. Dauterman, Stephen G. Ellis, The Cleveland Clinic Foundation, Cleveland, OH

Background: An elevated baseline C-reactive protein (CRP) prior to PCI has been associated with worse outcomes at 30 days; however, the longer term prognostic significance of an elevated value is not well established. We sought to determine if an elevated baseline CRP prior to PCI impacts long-term outcomes at 1-year. **Methods:** Using a single-center interventional registry database, we identified 1644 consecutive PCI patients in whom baseline pre-procedural CRP values were prospectively collected. Patients were divided into 4 quartiles (Q) based on CRP value (in mg/dl): Q1<0.16, Q2=0.16-0.40, Q3=0.41-1.10, and Q4>1.10. One year outcome data, including death and MI, were collected on all patients. **Results:** For each increasing quartile of CRP, there was a significantly increased risk of death (Figure) and death/MI at one year (death-X^2=66, p<0.0001; death/MI-X^2=43, p<0.0001). Using a Cox proportional hazards model to adjust for confounding by age, lesion score, LVEF, ACS, renal insufficiency, BMI, and statin therapy, baseline CRP remains a significant predictor of 1-year death or MI (HR=1.24 [CI=1.08-